Early release, published at www.cmaj.ca on September 20, 2010. Subject to revision.

Influenza vaccination, pneumococcal vaccination and risk of acute myocardial infarction: matched case–control study

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Abstract

Background: Previous studies have shown an association between acute myocardial infarction and preceding respiratory infection. Contradictory evidence exists on the influence of influenza vaccination and pneumococcal vaccination in preventing cardiovascular disease. We aimed to investigate the possible association of influenza vaccination and pneumococcal vaccination with acute myocardial infarction.

Methods: We used a matched case–control design with data from the United Kingdom General Practice Research Database. Cases were patients who were at least 40 years of age at diagnosis of first acute myocardial infarction recorded from Nov.1, 2001, to May 31, 2007, and were matched for sex, general practice, age and calendar time (i.e., month corresponding to index date of acute myocardial infarction), with up to four controls each. Data were analyzed using conditional logistic regression, adjusted for vaccination target groups, cardiovascular risk factors, treatment medications and attendances at a general practice.

Results: We included 78 706 patients, of whom 16 012 were cases and 62 694 were matched controls. Influenza vaccination had been received in the previous year by 8472 cases (52.9%) and 32 081 controls (51.2%) and was associated with a 19% reduction in the rate of acute myocardial infarction (adjusted odds ratio [OR] 0.81, 95% confidence interval [CI] 0.77–0.85). Early seasonal influenza vaccination was associated with a lower rate of acute myocardial infarction (adjusted OR 0.79, 95% CI 0.75–0.83) than vaccination after mid-November (adjusted OR 0.88, 95% CI 0.79–0.97). Pneumococcal vaccination was not associated with a reduction in the rate of acute myocardial infarction (adjusted OR 0.96, 95% CI 0.91–1.02).

Interpretation: Influenza vaccination but not pneumococcal vaccination is associated with a reduced rate of first acute myocardial infarction. This association and the potential benefit of early seasonal vaccination need to be considered in future experimental studies.

DOI:10.1503/cmaj.091891

Winter peaks in incidence of acute myocardial infarction have been linked to climate,[1] metabolic factors[2] and infection.[3] Because known risk factors do not fully account for cases of acute myocardial infarction, current interest is focused on the putative link with respiratory infection. Significant increases in acute myocardial infarction occur during peak winter incidence of pneumonia, influenza and influenza-like syndrome,[4] particularly during years dominated by epidemic rather than nonepidemic influenza A. This association supports the notion that the increase is caused by influenza rather than cold weather.[5]

Acute myocardial infarction may increase susceptibility to respiratory illness,[6] but the association between acute myocardial infarction and respiratory infection occurring within four weeks prior to the acute myocardial infarction[7,8] supports infection as a cause of acute myocardial infarction. Although the exact mechanism is unknown, the favoured hypothesis is that infection triggers plaque rupture.[9] Although several observational studies, as well as two randomized controlled trials,[10,11] suggest a positive effect of influenza vaccine in preventing acute myocardial infarction, they provide insufficient and conflicting evidence.[12]

The aim of this study was to investigate a possible association between influenza or pneumococcal vaccination and acute myocardial infarction.

Methods

Study design and ethics approval

We used a matched case–control study design. Each case of acute myocardial infarction was matched to four controls according to age, sex, general practice attended and calendar time (i.e., month corresponding to index date of acute myocardial infarction), using incidence density sampling according to person-time at risk.[13] The study was approved by the Independent Scientific Advisory Committee of the General Practice Research Database and the United Kingdom National Research Ethics Service.

Data sources

Data were extracted from the General Practice Research Database, an extensively validated computerized database, representative of and comprising 5% of the population of England and Wales.[14] Virtually all patients in the database are

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CMAJ 2010. DOI:10.1503/cmaj.091891

registered with a general practitioner, and all health care attendances are recorded in the database. The database contains reliable, anonymized patient data that includes demographic information, diagnoses, medication, health-related behaviours, referrals and treatment outcomes.

We estimated that 6176 cases and 24 704 controls would provide 90% power to detect an odds ratio (OR) of 0.9 using a two-sided 5% significance level, assuming 70% of controls were vaccinated and with a correlation coefficient of 0.2 between cases and matched controls for a clinically important effect based on current vaccination rates.[15] All available cases in the General Practice Research Database were included in the study.

Selection of cases and controls

Case patients were at least 40 years of age at the time of diagnosis of first acute myocardial infarction (fatal or nonfatal) had clinical records for over five and a half years (between Nov. 1, 2001, to May 31, 2007) and were identified using standardized (Read and Oxford Medical Information Systems [OXMIS]) codes. The date of acute myocardial infarction, referred to as the index date, was used to match controls. Four controls were selected at random from the eligible matched controls for each case (i.e., before exposure status was known). We included only cases and controls with clinical records for at least five years before the index date to ensure completeness of recording of exposures and confounding variables.

Identification of vaccination status

Only data on influenza and pneumococcal vaccinations administered before the index date were extracted. For the main analyses, influenza vaccination was defined as vaccination given in the year preceding the index date. Other exposures to influenza vaccination considered were influenza vaccination within the current vaccination season (i.e., the same vaccination season as the index date) and early (i.e., between Sept. 1 and Nov. 15) or late vaccination (i.e., between Nov. 16 and Feb. 28 or 29, depending on the year).

Patients were considered to have had a pneumococcal vaccination if they had ever received the pneumococcal vaccine before the index date. Combined vaccination was defined as pneumococcal vaccination ever combined with influenza vaccination in the year preceding the index date.

Confounding variables

Data on potential confounding variables were extracted using Read and OXMIS codes recorded before the index date (Table 1). High-risk categories and target groups are identical for pneumococcal and influenza vaccination,[15] as defined by the UK Department of Health (2008).

Statistical analysis

Conditional logistic regression was used to estimate unadjusted and adjusted ORs and 95% confidence intervals (CIs) for the association between acute myocardial infarction and influenza and pneumococcal vaccination. Since we used incident patient cases who were matched with controls, were free of disease at the end of the study period and were from a dynamic population, ORs were taken as estimating rate ratios.[13]

The adjusted analyses accounted for confounders, including target groups for vaccination, additional cardiovascular risk factors, treatments and general practitioner consultations in the preceding five years, grouped into four categories based on quartiles of the distribution (≤ 12, 13–26, 27–44, and ≥ 45). Smoking status was known for most patients (92%) and included in the main analyses; patients whose smoking status was unknown were excluded. Each type of vaccination was adjusted for the other type.

Trends were established using likelihood ratio tests for trend. Subgroup analyses using likelihood ratio tests for interaction were conducted for age (< 65 and ≥ 65 years) and vaccination target group (at least one target group present).

Systolic blood pressure, body mass index (BMI) and total cholesterol were not included in the main adjusted analyses owing to missing data (63%, 45% and 15% completeness respectively). To replace missing values for smoking status, systolic blood pressure, BMI and total cholesterol, multiple imputation was conducted as an additional analysis,[16] creating ten imputed data sets with results combined using Rubin's rules to account for uncertainty in the imputed data.[17]

Results

We included 16 012 cases and 62 964 matched controls from 379 practices. Most cases (95.7%) had four controls. Confounding factors, apart from splenectomy and chronic liver disease, were reported more frequently in cases than controls (Table 1).

People with risk factors for acute myocardial infarction were more likely to be vaccinated (Table 2), which was expected since many cardiovascular risk factors are also indications for vaccination.

Influenza vaccination and acute myocardial infarction

Uptake of the influenza vaccine and results of the conditional logistic regression are shown in Table 3. The unadjusted analyses showed a slightly increased risk of acute myocardial infarction in vaccinated people. However, this analysis does not account for the fact that vaccinated people make up a preselected group and are already at increased risk for acute myocardial infarction because of their risk factors (unadjusted OR for acute myocardial infarction among people in a high-risk group is 2.26 (95% CI 2.18 to 2.35).

After adjusting for confounding variables, so that vaccinated and unvaccinated groups were comparable in terms of risk factors in the model, we found that influenza vaccination within the previous year was associated with a significantly reduced rate of acute myocardial infarction (adjusted OR 0.81, 95% CI 0.77 to 0.85, $p < 0.001$).

The confounders that contributed most to the change in OR for influenza vaccination were consultation rate, previous coronary heart disease and diabetes mellitus. Number of consultations before acute myocardial infarction was a key variable in the adjusted analysis; patients with more consultations were more likely to receive vaccination, but were also at increased risk of acute myocardial infarction — presumably

Table 1: Characteristics of cases and controls

Characteristic	No. (%)* Cases *n = 16 012*	Controls *n = 62 694*	Unadjusted OR (95% CI)
Matching variables			
Age, yr			
40–64	5 341 (33.4)	21 359 (34.1)	NA†
≥ 65	10 671 (66.6)	41 335 (65.9)	NA†
Sex			
Male	6 168 (38.5)	24 171 (38.5)	NA†
Female	9 844 (61.5)	38 523 (61.5)	NA†
Vaccination target groups			
Asthma or COPD attack, ever	1 980 (12.4)	5 803 (9.3)	1.39 (1.32–1.47)
Chronic heart disease	3 756 (23.5)	6 174 (9.9)	2.97 (2.83–3.11)
Stroke or transient ischemic attack	1 434 (9.0)	3 487 (5.6)	1.66 (1.56–1.78)
Diabetes	2 451 (15.3)	5 637 (9.0)	1.85 (1.76–1.95)
Splenectomy	36 (0.2)	116 (0.2)	1.24 (0.85–1.80)
Chronic liver disease	30 (0.2)	93 (0.2)	1.26 (0.83–1.90)
Chronic renal disease	584 (3.7)	724 (1.2)	3.30 (2.94–3.69)
Immunosuppression or HIV	2 (0.01)	3 (< 0.01)	2.67 (0.45–15.96)
Other cardiovascular risk factors			
Hyperlipidemia	2 180 (13.6)	5 835 (9.3)	1.61 (1.52–1.70)
Family history of myocardial infarction	302 (1.9)	954 (1.5)	1.29 (1.12–1.48)
BMI recorded within past 3 yr	8 072 (50.4)	27 434 (43.8)	
BMI kg/m^2, mean (SD)	27.3 (5.2)	27.0 (4.9)	1.11‡ (1.04–1.17)
Peripheral vascular disease	1 216 (7.6)	2 084 (3.3)	2.42 (2.25–2.61)
Hypertension	6 211 (38.8)	19 538 (31.2)	1.45 (1.40–1.51)
Smoking history			
Never smoked	6 292 (39.3)	31 000 (49.4)	1.00
Ex-smoker	4 543 (28.4)	1 545 (25.1)	1.49 (1.42–1.56)
Current smoker	4 265 (26.7)	10 263 (16.4)	2.22 (2.12–2.33)
Not recorded	912 (5.7)	5 686 (9.1)	
Systolic blood pressure recorded in past yr	11 945 (74.6)	37 338 (59.6)	
Systolic blood pressure mmHg, mean (SD)	140.5 (21.4)	141.4 (18.0)	0.98‡ (0.96–0.99)
Total cholesterol recorded	2 823 (17.6)	9 150 (14.6)	
Total cholesterol mmol/L, mean (SD)	5.37 (1.27)	5.28 (1.13)	1.04§ (1.00–1.09)
Treatments			
Treatment with ASA (≥ 2 prescriptions in previous 6 mo)	1 892 (11.8)	5 211 (8.3)	1.52 (1.44–1.62)
Treatment with statins (≥ 1 prescriptions in previous yr)	1 817 (11.4)	4 372 (7.0)	1.79 (1.69–1.90)
Treatment with antihypertensives (≥ 1 prescriptions in previous yr)	1 032 (6.5)	2 468 (3.9)	1.72 (1.59–1.85)
No. of GP consultations in last 5 yr			
≤ 12	3 031 (18.9)	17 196 (27.4)	1.00
13–26	3 749 (23.4)	16 618 (26.5)	1.37 (1.30–1.45)
27–44	4 193 (26.2)	15 061 (24.0)	1.79 (1.69–1.89)
≥ 45	5 039 (31.5)	13 819 (22.1)	2.48 (2.34–2.63)

Note: ASA = acetylsalicylic acid, BMI = body mass index, CI = confidence interval, COPD = chronic obstructive pulmonary disease, GP = general practitioner, NA = not applicable, OR = odds ratio, SD = standard deviation.
*Unless otherwise indicated.
†Variables that were matched and hence not applicable.
‡Per 10-unit increase.
§Per unit increase.

because they were sicker and hence consulting physicians more often. Adjusting for consultation rate alone resulted in an OR for vaccination of 0.84 (95% CI 0.80 to 0.88). However, when we adjusted for all other confounders except consultations, influenza vaccination was still protective (OR 0.87, 95% CI 0.83 to 0.91).

When the association between acute myocardial infarction and influenza vaccination in the last year was further adjusted for "ever receiving pneumococcal vaccination," the result was an adjusted OR of 0.82 (95% CI 0.78 to 0.86). Vaccination within the current vaccination season was also associated with a significantly reduced rate of acute myocardial infarction (adjusted OR 0.80, 95% CI 0.76 to 0.84, $p < 0.001$). Most vaccinations administered were given early, between September and mid-November (90.3% in cases and 91.0% in controls). When compared with no vaccination, early vaccination was associated with a 21% reduction in the rate of acute myocardial infarction, whereas late vaccination was associated with a 12% reduction. Compared with late vaccination, early vaccination was associated with a significantly reduced rate of acute myocardial infarction (adjusted OR 0.90, 95% CI 0.82 to 1.00, $p = 0.042$). Influenza vaccination was associated with a significantly reduced rate of acute myocardial infarction in all periods. There was no significant reduction in acute myocardial infarction when the last vaccination was given more than a year before the index date.

Repeated vaccination (i.e., vaccination in all previous five or six consecutive seasons) was associated with a significant reduction in the rate of acute myocardial infarction (adjusted OR 0.79, 95% CI 0.74 to 0.84) compared with no vaccinations in the previous five years, as was vaccination within the current season (OR 0.85, 95% CI 0.80 to 0.90), but not consecutively in the five or six preceding vaccination seasons.

We conducted separate analyses and tests for interaction according to vaccination target group (i.e., with at least one target group present). The association between influenza vaccination and acute myocardial infarction was more marked for those in a vaccination target group (adjusted OR 0.70, 95% CI 0.64 to 0.77) compared with those not in a target group (adjusted OR 0.85, 95% CI 0.79 to 0.91, test for interaction $p < 0.001$).

In the analyses using multiply imputed data with BMI, systolic blood pressure and total cholesterol added to the covariates, the adjusted OR for influenza vaccination in the previous year was 0.83 (95% CI 0.80 to 0.88).

Pneumococcal vaccination and acute myocardial infarction

Just over one-third of cases (35.4%) and controls (34.7%) had received a pneumococcal vaccination before the index date (Table 4), and almost all of these (27 257 of 27 887) had been vaccinated within 10 years of the index date.

When adjusted for all covariates including influenza vacci-

Table 2: Distribution of risk factors for acute myocardial infarction by vaccination

Risk factor	No. (%)*			
	No vaccination *n = 35 244*	Influenza vaccination only *n = 15 575*	Pneumococcal vaccination only *n = 2 909*	Combined vaccination *n = 24 978*
Chronic heart disease	2 026 (5.8)	2 111 (13.6)	586 (20.1)	5 207 (20.9)
Stroke or TIA	1 103 (3.1)	1 150 (7.4)	268 (9.2)	2 400 (9.6)
Diabetes	1 392 (4.0)	1 430 (9.2)	561 (19.3)	4 705 (18.8)
Asthma or COPD	1 583 (4.5)	1 466 (9.4)	500 (17.2)	4 234 (17.0)
Chronic liver disease	43 (0.1)	25 (0.2)	12 (0.4)	43 (0.2)
Chronic renal disease	240 (0.7)	245 (1.6)	118 (4.1)	705 (2.8)
Splenectomy	22 (0.1)	3 (0.02)	30 (1.0)	97 (0.4)
Hypertension	7 345 (20.8)	5 822 (37.4)	1 203 (41.4)	11 379 (45.6)
Peripheral vascular disease	824 (2.3)	680 (4.4)	173 (6.0)	1 623 (6.5)
Hyperlipidemia	2 358 (6.7)	1 605 (10.3)	366 (12.6)	3 686 (14.8)
Current smoker	8 671 (28.6)	2 438 (16.7)	480 (17.2)	2 939 (12.1)
Obesity or overweight	7 900 (22.4)	4 595 (29.5)	999 (34.3)	9 689 (38.8)
Treatment with antihypertensives	949 (2.7)	672 (4.3)	173 (6.0)	1 706 (6.8)
Treatment with statins	1 486 (4.2)	1 263 (8.1)	319 (11.0)	3 121 (12.5)
Treatment with ASA	1 601 (4.5)	1 458 (9.4)	350 (12.0)	3 694 (14.8)
Family history of AMI	531 (1.5)	261 (1.7)	43 (1.5)	421 (1.7)
Average no. GP consultations in the past 5 yr, mean (95% CI)	19.3 (19.1–19.5)	36.3 (35.9–36.7)	41.1 (40.0–42.2)	44.9 (44.6–45.3)

Note: AMI = acute myocardial infarction, ASA = acetylsalicylic acid, CI = confidence interval, COPD = chronic obstructive pulmonary disease, GP = general practitioner, TIA = transient ischemic attack.
*Unless otherwise indicated.

nation, there was no significant effect of pneumococcal vaccination (adjusted OR 0.96, 95% CI 0.91 to 1.02). Using multiply imputed data and also adjusting for BMI, systolic blood pressure and total cholesterol, the adjusted OR for pneumococcal vaccination was 0.98 (95% CI 0.93 to 1.04). Combined influenza and pneumococcal vaccination did not show significant benefit when compared with influenza vaccination alone (adjusted OR 0.94, 95% CI 0.89 to 1.01, $p = 0.07$).

Table 3: Association between influenza vaccination and acute myocardial infarction

Characteristic	No. (%)		OR (95% CI)		
	Cases *n = 16 012*	Control *n = 62 694*	Unadjusted	Adjusted*	Multiply imputed data, adjusted†
Vaccination in preceding yr					
All ages (≥ 40 yr)	8 472 (52.9)	32 081 (51.2)	1.08 (1.04–1.13)	0.81 (0.77–0.85)	0.83 (0.80–0.88)
< 65 yr	1 035 (19.4)	3 166 (14.8)	1.41 (1.30–1.53)	0.81 (0.73–0.90)	0.83 (0.75–0.92)
≥ 65 yr	7 437 (69.7)	28 915 (70.0)	0.99 (0.94–1.04)	0.79 (0.75–0.83)	0.82 (0.78–0.86)
Time since last vaccination at index date, mo					
Never vaccinated	5 842 (36.5)	25 423 (40.6)	1.00	1.00	1.00 (0.78–0.90)
0–3	3 187 (19.9)	12 395 (19.8)	1.16 (1.09–1.24)	0.80 (0.74–0.86)	0.84 (0.80–0.94)
3–6	2 230 (13.9)	8 354 (13.3)	1.22 (1.13–1.32)	0.82 (0.76–0.89)	0.86 (0.85–0.99)
6–12	3 055 (19.9)	11 332 (18.1)	1.27 (1.19–1.36)	0.87 (0.81–0.94)	0.91 (1.06–1.24)
12–60	1 447 (9.1)	4 270 (6.8)	1.55 (1.45–1.67)	1.12 (1.03–1.21)	1.15 (0.88–1.20)
≥ 60	251 (1.6)	920 (1.5)	1.21 (1.05–1.40)	0.96 (0.82–1.13)	1.03
Within-season vaccination					
Yes	7 496 (46.8)	28 487 (45.4)	1.07 (1.02–1.12)	0.80 (0.76–0.84)	0.83 (0.79–0.87)
Early within-season (Sept. to mid-Nov.)	6 770 (42.3)	25 911 (41.3)	1.07 (1.01–1.11)	0.79 (0.75–0.83)	0.82 (0.78–0.86)
Late within-season (mid-Nov. to Feb.)	726 (4.5)	2 571 (4.1)	1.16 (1.05–1.27)	0.88 (0.79–0.97)	0.90 (0.82–1.00)
Vaccination in previous yr, by mo of index date					
Sept. to Nov.	1 744 (46.8)	6 862 (47.0)	0.97 (0.89–1.06)	0.75 (0.68–0.83)	0.77 (0.70–0.85)
Dec. to Mar.	3 418 (55.6)	12 761 (53.1)	1.13 (1.06–1.21)	0.86 (0.79–0.93)	0.88 (0.82–0.95)
Apr. to Aug.	3 310 (53.9)	12 458 (51.8)	1.11 (1.03–1.19)	0.80 (0.73–0.86)	0.84 (0.77–0.90)

Note: CI = confidence interval, OR = odds ratio.
*Adjusted for asthma or chronic obstructive pulmonary disease, chronic heart disease, stroke or transient ischemic attack, diabetes, splenectomy, chronic liver disease, chronic renal failure, immunosuppression and HIV, hyperlipidemia, family history of acute myocardial infarction, peripheral vascular disease, hypertension, smoking status, treatment with acetylsalicylic acid, treatment with statins, treatment with antihypertensives, and general practice consultations.
†Adjusted for all of the above variables as well as for body mass index, systolic blood pressure and total cholesterol using 10 multiply imputed data sets.
‡Totals for the period of Sept. to Nov. were 3723 cases and 14 599 controls. Totals for the period of Dec. to Mar. were 6146 cases and 24 036 controls. Totals for the period of Apr. to Aug. were 6143 cases and 24 059 controls.

Table 4: Association between pneumococcal vaccination and acute myocardial infarction

Ever received pneumococcal vaccination, age, yr	No. (%)		OR (95% CI)		
	Cases	Controls	Unadjusted	Adjusted* (except for influenza vaccination)	Adjusted* (including for influenza vaccination)
All ages (≥ 40)	6 153 (35.4)	21 734 (34.7)	1.26 (1.20–1.32)	0.88 (0.84–0.93)	0.96 (0.91–1.02)
< 65	622 (11.7)	1 600 (7.5)	1.67 (1.51–1.84)	0.83 (0.73–0.95)	0.91 (0.79–1.05)
≥ 65	5 531 (51.8)	20 134 (48.7)	1.18 (1.12–1.24)	0.88 (0.83–0.93)	0.97 (0.91–1.03)

Note: CI = confidence interval, OR = odds ratio.
*Adjusted for asthma or chronic obstructive pulmonary disease, chronic heart disease, stroke or transient ischemic attack, diabetes, splenectomy, chronic liver disease, chronic renal failure, immunosuppression and HIV, hyperlipidemia, family history of acute myocardial infarction, peripheral vascular disease, hypertension, smoking status, treatment with acetylsalicylic acid, treatment with statins, treatment with antihypertensives, and general practice consultations.

Interpretation

Influenza vaccination within the past year was associated with a 19% reduction in the rate of acute myocardial infarction among patients aged 40 years and over. Influenza vaccination administered within influenza season was also associated with a significant reduction (20%) in the rate of acute myocardial infarction. We found that early vaccination within the influenza season (i.e., September to mid-November) was associated with greater benefit than vaccination later in the season (21% v. 12% reduction in the rate of acute myocardial infarction compared with no vaccination). Pneumococcal vaccination or combined vaccination had no additional benefit compared with influenza vaccination alone.

Unsurprisingly, cases and controls were different in their disease and treatment characteristics, with cases more likely to have comorbidities or be receiving treatment than controls. Cases were more likely to have been vaccinated than controls, particularly those between age 40 and 64 years, a finding that accords with current UK guidelines to vaccinate all those in a target group. Importantly, we found that multivariate adjustment for confounding factors led to a protective association for influenza vaccination.

Convincing evidence of a protective role for influenza infection is emerging. Our findings lend support to previous evidence from observational studies of primary prevention[10] and randomized studies of secondary prevention[11] suggesting a beneficial effect of influenza vaccination for prevention of acute myocardial infarction or its complications. Previous observational studies have been limited by methodologic problems, including recall bias in self-reported vaccination status.[10,18] Studies with no evidence of benefit had low power, poor case ascertainment, misclassification of vaccination status and lack of investigator blinding.[19–21] The additional benefit of early within-season influenza vaccination (i.e., during the period from September to mid-November) compared with late vaccination (i.e., after mid-November) has been suggested by findings of previous research,[22] but is not part of current recommendations for influenza vaccination.[23]

Given that influenza vaccination is likely to be effective only against circulating strains of influenza virus, our findings are strengthened by the biological plausibility of a within-season or within-year effect of influenza vaccination in preventing influenza-related acute myocardial infarction. The finding that influenza vaccination was associated with a reduction in the risk of acute myocardial infarction, whereas no effect was found for pneumococcal vaccination, is evidence against the explanation that unknown confounders constituted a "healthy user" effect. If the 12-month protective effect of influenza vaccination was a result of confounding by indication, then we would also expect to find a protective effect for influenza vaccination beyond 12 months and for pneumococcal vaccination by the same token. But we did not. We believe that this discrepancy also supports the plausibility of our findings, and that the difference between the effect of early versus late vaccination on the risk of acute myocardial infarction cannot be explained by confounding by indication. Influenza vaccination was beneficial regardless of the month of acute myocardial infarction. This finding could be an indication of longer-term benefits for prevention of influenza infection, given that vaccinations considered in this instance had been given in the preceding 12 months. Following biological explanations for the association between acute myocardial infarction and influenza, the flu virus would have had a lesser effect on the vaccinated patients' circulatory systems.

Although previous studies have shown an additive effect of pneumococcal vaccination for prevention of respiratory disease,[24] we did not find a reduction in the rate of acute myocardial infarction for pneumococcal vaccination after adjusting for influenza vaccination, even among people aged 65 years and over. Our findings contrast with those of a recent study suggesting that pneumococcal vaccination was associated with a 50% reduction in the rate of acute myocardial infarction.[25] Investigators in that study did not account for differences in cardiovascular risk factors, nor, crucially, for the confounding effect of influenza vaccination.

Strengths and limitations

Despite their known problems of bias and confounding, case–control designs are efficient in examining the association between outcomes and exposures. The large General Practice Research Database sample provided good power to investigate associations in a representative population with precision. We minimized selection bias by including all cases of acute myocardial infarction within the selected time period and matched controls, free of the outcome of interest and independent of the exposure of interest.[26] Matching for age, sex, practice and calendar time (month corresponding to index date of acute myocardial infarction) increased the precision of our results compared with those of previous, unmatched case–control studies. Information on exposures was recorded before the index date, eliminating recall bias.

To minimize bias due to misclassification and missing data, patients were selected only if they had at least five years of up-to-standard data on the General Practice Research Database. To reduce confounding from "healthy user," "indication" or "treatment" biases, we adjusted for many known confounders, including vaccination target groups and cardiovascular risk groups, treatments and general practitioner consultation rate, of which the latter is thought to be related to functional and economic status.[27] Potential confounders such as functional status were not fully accounted for because of unavailability of data, and we did not have data for other triggers, such as stressful life events. Although we observed missing values for variables such as smoking status, systolic blood pressure, BMI and total cholesterol, we used standard imputation procedures to account for these and obtained results similar to those of our complete case analysis.

Conclusion

Our findings reinforce current recommendations for annual influenza vaccination of target groups,[23,28] with a potential added benefit for prevention of acute myocardial infarction in those without established cardiovascular disease.[29] This benefit may lead to an increase in suboptimal rates of vaccination, particularly among younger patients.[15]

Further research is needed to confirm our finding that early vaccination, in particular, confers additional reduction in risk for acute myocardial infarction. If substantiated, this finding has implications for timely supply and administration of influenza vaccine and could lead to changes in recommendations for timing of vaccination.

This article has been peer reviewed.

Competing interests: None declared.

Contributors: Niroshan Siriwardena had the initial idea for the study and received support in the conception and design of the study from Carol Coupland. Stella Gwini was involved in the design of the study, performed the analysis of the data supported by Carol Coupland, and wrote the first draft of the article. All of the authors interpreted the results, participated in reviewing and revising the manuscript, and approved the final version of the manuscript submitted for publication.

Acknowledgements: The authors thank Prof. Tom Meade and Mr. Tim Clayton of the London School of Hygiene and Tropical Medicine for their support and advice, and the General Practice Research Database for providing data for the study.

Funding: This study was supported by funding from the Research for Patient Benefit Program of the National Institute for Health Research, United Kingdom [PB-PG-0706–10449] and was conducted independently from the funding body. The sponsor had no role in the design of the study, the collection, analysis or interpretation of the data, the writing of the manuscript or the decision to submit the study for publication. Niroshan Siriwardena had full access to all of the data and final responsibility for the decision to submit the study for publication.

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